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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|---------------------------|---------------------|------------------|
| 10/538,200 | 06/09/2005 | Donatienne Denni-Dischert | ON/4-32823A | 1807 |
| 1095 | 7590 | 02/26/2007 | EXAMINER | |
| NOVARTIS CORPORATE INTELLECTUAL PROPERTY ONE HEALTH PLAZA 104/3 EAST HANOVER, NJ 07936-1080 | | | RAHMANI, NILOOFAR | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1625 | |
| SHORTENED STATUTORY PERIOD OF RESPONSE | | MAIL DATE | DELIVERY MODE | |
| 3 MONTHS | | 02/26/2007 | PAPER | |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| | | | |
|------------------------------|------------------------|-----------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/538,200 | DENNI-DISCHERT ET AL. | |
| | Examiner | Art Unit | |
| | Niloofar Rahmani | 1625 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 09 June 2005.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-7 and 10-22 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) 11-14 is/are allowed.
- 6) Claim(s) 1-7, 10 and 15-22 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-7, 10-22 are currently pending in the instant application and claims 8-9 are cancelled.

Priority

2. This application is filed on 06/09/2005, which is a 371 of PCT/EP03/14747, filed on 12/22/2003, which claims priority of UNITED KINGDOM 02300242, filed on 12/23/2002.

3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,7, 10 and 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1,7,10 are rejected because the term " R" is confusing. On line 17 of the claim 1, the term "R" is vague and ambiguous because it appears that applicant intended this term to be "R₁" as found in formula (I). Correction is required.

4. Claims 15-16 are rejected because of the term "C4-desmethyl-epothilone B" is confusing. What is the formula of "C4-desmethyl-epothilone B"? It is recommended to insert the formula of "C4-desmethyl-epothilone B".

5. Claims 15-16 are rejected because the term " Chiralpak-AD column" is confusing. What is " Chiralpak-AD column"? Correction is required.

6. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph. The claims lack written description for microorganism. What species of the microorganism make the compound with the certain deposit #? Does the species of the microorganism in all conditions make the instantly claimed compound? Due to this, the specification lacks description of "microorganism".

7. *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph. The claims lack operable steps and parameter. The claims encompassed any and all conditions for producing the compound of formula (I), for which insufficient description was found in the specification.

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To satisfy the enablement requirement a deposit must be made "prior to issue" but need not be made prior to filing the application. *In re Lundak*, 773 F.2d 1216, 1223, 227 USPQ 90, 95 (Fed. Cir. 1985).

Claim 16 is drawn to microorganism with no limitation to the species. There is no record for any deposit in the prosecution record. What species in the genus "microorganism" makes the compound or do the entire genus "microorganism" make the compound? Under what conditions is this compound made? If so, then enablement is needed for that. Any species embraced by the genus including future development must be deposited in compliance with MPEP§ 2404.

8. Claims 10 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy

the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The nature of the invention: The instant invention is drawn to a method for treatment of warm-blooded animals suffering from a tumor disease using a compound of formula in claim 1.

The state of the prior art: Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single

extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (*Culture of Animal Cells, A Manual of Basic Technique*, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. Further, although drawn specifically to cancer cells, Dermer (*Bio/Technology*, 1994, 12:320) teaches that, "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the

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contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

The predictability in the art: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

Amount of guidance/working examples: On pages 38-39 of the specification, applicant has examples of test compounds for inhibition of microtubule depolymerisation. However, applicant has no guidance or examples for treating tumor disease.

The breadth of the claims: The breadth of claims is drawn a method for treatment of warm-blooded animals suffering from a tumor disease using a compound of formula in claim 1.

The quantity of undue experimentation needed: Since the guidance and teaching provided by the specification is insufficient for treating tumor disease,

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one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claims 10 and 22, for treating tumor disease, have been enabled by the instant specification.

9. *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless —

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 10 and 17-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Hardt et al., Journal of Natural Products, 2001, Vol. 64, pages 847-856. Hardt et al. disclosed the instant claimed compounds and compositions on page 849

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Epothilone A₁ (5) [479], Epothilone A₂ (6) [479], trans-Epothilone C₁ (28) [463], trans-Epothilone C₂ (29) [463], which using as anticancer agents. Therefore, the instant claim is anticipated by Hardt et al.

10. Claims 1-7, 10 and 17-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardt et al., WO 9965913. Hardt et al. disclosed the instant claimed compounds and compositions on page 2
Epothilone A₁ (5) , Epothilone A₂ (6) , Epothilone G₁ (10), Epothilone G₂ (11), Epothilone C₁ (16) ,Epothilone C₂ (18), which using as anticancer agents.
Therefore, the instant claim is anticipated by Hardt et al.

11. *Allowable Subject Matter*

Claims 11-14 are patentable over Hardt et al., WO 9965913. The reference does not teach the instant compounds and process. Therefore, the claims are free of prior art.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas Mckenzie, can be reached on 571-272-0670. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR.

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Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

02/13/2007





MARGARET SEAMAN

PRIMARY EXAMINER

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